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| 09/712,819 | 11/13/2000 | Fred J. Stevens | 0003/00537 | 9146 |

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| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/712,819 | STEVENS ET AL. | |
| | Examin r | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *2/6/03; 2/10/03; 4/8/03; 7/21/03* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disp sition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, and 15-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

**DETAILED ACTION**

1. It is noted that claim 14 was inadvertently left out in the pending claims in previous Office Action. Claim 14 was withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

2. Claims 1-22 are pending.

3. Claim 14 stands withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. The affidavit filed on 2/6/03 under 37 CFR 1.131 has been considered but is ineffective to overcome the Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892) reference.

The evidence submitted is insufficient to establish a reduction to practice of the invention in this country prior to the effective date of the Davids reference because (1) the scope of the affidavit is not commensurate with the scope of the claims and (2) missing the signatures of inventors Yair Argon, David P. Davis and Rosemarie Raffen.

5. In view of the amendments filed 2/6/03, 2/10/03, 4/8/03 and 7/21/03, the following objection and rejections remain.

6. The disclosure stands objected to because of the following informality: SEQ ID NO is required for peptide such as the ones disclosed on page 3, 5, 6, 8, 9, 10 and 15. Appropriate action is required. Although Applicants have provide a clean copy of the specification to be substitute, it is noted that the clean copy of the specification is missing pages 2-8, and 10-12 missing. Further, other peptides such as the ones disclosed on page 3, 5, 6, 8, 9, 10 and 15 also require SEQ ID NO.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-13, and 15-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain in vitro as set forth in claims 21 and 22, and a method for minimizing the aggregation of amyloid forming protein, the method comprising: a) identifying SMA or LEN mutation in the amino acid sequence of said protein that leads to fibril formation; b) substituting each mutation for Ala or proline into said LEN or SMA to identify the residues of a peptide that contribute to fibril formation; c) synthesizing peptides spanning most of the light chain variable region that interacts with an endoplasmic reticulum chaperone selected from the group consisting of Bip, Hsp 70 and combinations thereof; d) determining the VL-derived peptides for their ability to inhibit fibril formation in vitro wherein the peptides are selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKSR (SEQ ID NO: 13) and combination thereof and e) inhibiting fibril formation by inserting the said peptide in to the light chain variable domain, (2) The said method wherein the method is conducted in a cell, (3) the said method wherein the amyloid forming protein is humankappa-4 light chain variable domain, or a greek key fold protein selected from the group consisting of antibody constant domains, transthyretin, and beta-2 microglobulin, and crystalline, (4) the said method wherein the peptide amino acid sequence is identical to an amino acid sequence in a region f the light chain variable domain, (5) the said method wherein the peptide is inserted between residue position numbers 60 and 83 of the human kappa-IV light chain, (6) the said method wherein the peptide consisting of the amino acid sequence Phe71-Thr72-Leu73-Thr74-Ile75-Ser76-Ser77 (SEQ ID NO: 1) and wherein the subscript denote the positions of the amino acids in the light chain variable domain, (7) the said method wherein said the peptide is inserted when the amyloid forming protein is partially unfolded, (8) the said method wherein the peptide is inserted at a hairpin anchorage point in the greek key fold protein, (9) the said method wherein the peptide is a target for an endoplasmic reticulum chaperone, (10) The said method wherein the peptide is inserted at a hairpin anchorage point in the human kappa-IV protein and its derivatives selected from the group consisting of SEQ ID NO: 5, 1, 6, 12, 13 and combination thereof, (11) The said method wherein the peptide is an endoplasmic reticulum chaperon selected from the group consisting of hsp 70 and BiP, (12) the said method wherein the peptide interacts with endoplasmic reticulum chaperone, the peptide selected from the group consisting of SEQ IDNO: 5, 1, 6, 11 and 12 to inhibit fibril aggregation in said cell by western blotting or

immunoflourosence, **does not** reasonably provide enablement for (1) a method for minimizing the aggregation tendencies of amyloid forming protein, the method comprising: a) identifying SMA or LEN mutation in the amino acid sequence of said protein that leads to fibril formation; b) substituting each mutation for Ala or proline into said LEN or SMA to identify the residues of a peptide that contribute to fibril formation; c) synthesizing peptides spanning most of the light chain variable region that interacts with an endoplasmic reticulum chaperone selected from the group consisting of Bip, Hsp 70 and combinations thereof; d) determining the VL-derived peptides for their ability to inhibit fibril formation in vitro wherein the peptides are selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKSR (SEQ ID NO: 13) and combination thereof and e) **preventing** fibril or amyloid formation by inserting the said peptide in to the light chain variable domain, as set forth in claims 1-13, 15 and 16 and (2) a method for **preventing** fibril assembly of human kappa-IV immunoglobulin as set forth in claims 17-22. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in *vitro* by identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, synthesizing peptides selected from the group consisting of spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, and determining the $V_L$-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEEQ ID NO: 13) for their ability to inhibit SMA fibril formation *in*

*vitro*. The specification further discloses a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprises identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, synthesizing peptides spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, expressing SMA or LEN in COS cells, treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEQ ID NO: 13) and determining the $V_L$-derived peptides for their ability to inhibit SMA fibril aggregation in said cell by western blotting or immunoflouresence.

The specification does not teach a method for minimizing the aggregation tendencies of *any* amyloid forming protein other than human kappa-4 immunoglobulin light chain (LC) because (1) the term "is" or "comprises" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is insufficient guidance and working examples as to which undisclosed amino acids to be added and (2) whether the resulting peptide when substitute into which undisclosed regions (residue numbers) of which undisclosed amyloid forming protein such as transthyretin, beta-2 microglobulin, *any* serine protease inhibitors and crystalline would prevent fibril formation in vitro or in a cell.

As to claim 4, there is insufficient guidance as to which region of the light chain variable domain the undisclosed peptide is identical to, let alone inserting the undisclosed peptide between residue position numbers of 60 and 83 of human kappa-IV light chain when the protein is partially unfolded.

As to claim 6, the term "domain" needs clarification because the domain could be any domain in any Greek key fold protein such as antibody constant domains, transthyretin, beta-2 microglobulin, serine protease inhibitors and crystalline. The specification discloses only that the peptide consisting of the amino acid sequence $Phe_{71}$-$Thr_{72}$-$Leu_{73}$-$Thr_{74}$-$Ile_{75}$-$Ser_{76}$-$Ser_{77}$ (SEQ ID NO: 1) and wherein the subscript denote the positions of the amino acids in the light chain variable domain. Further, there is insufficient guidance as to the full-length sequence of which protein that the subscripts denote.

As to claim 8, there is insufficient guidance as to the peptide such as SEQ ID NO: 5, 1, 6, 12 and 13 is identical in composition to which portion of which protein that anchors a hairpin-shaped amino acid sequence to which protein.

As to claim 11, given the inadequate guidance as to the structure of the peptide (amino acid sequence), it is unpredictable which undisclosed peptide is a target for endoplasmic reticulum chaperone such as hsp70 and BiP.

As to claim 15, it is not clear which domain that the peptide Phe-THr-Leu-Thr-Ile-Ser-Ser is supposed to be inserted into. Further, the peptide recited in claim 15 is only seven amino acids in length. The subscript numbering 71 through 77 denotes the residues of the light chain variable domain of the full-length protein. However, the SEQ ID NO of the full-length human kappa-IV light chain is not recited in the claim.

As to claim 19, there is insufficient guidance as to which binding protein that binds to which region of which amino acid sequence.

As to claims 1, 17, 21 and 22, it is not clear if "LEN" and "SMA" represent the specific amino acids in human kappa-IV light chain or the "LEN" and "SMA" represent the mutation in the human kappa-IV light chain. There is insufficient guidance as to (1) the amino acid sequence of "SMA" or "LEN" and (2) which amino acid within the undisclosed full length amino acid sequence of SMA or LEN to be substituted.

Stevens *et al*, of record, teach that amyloid is a generic term for the primarily extra cellular accumulation of fibrillar protein deposits and there are at least 20 unrelated, normally non-fibrillar proteins are known precursors of amyloid and each is associated with a specific disease (See page 443, in particular). Stevens *et al* further teach that in contrast to other proteins typically associated with amyloidosis, not all patients who overproduce light chains during myeloma experience development of clinically significant deposit, and no examples of light chains that differ at only a single amino acid position have been found today. Given the diversity of antibody light chains, a virtually unlimited number of variations, both inherited and acquired through somatic mutation can account fibril formation (See page 445, column 2, last paragraph, page 446, in particular). As such, it is unpredictable which undisclosed peptide and which amino acid substitutions within the undisclosed sequences of any Greek key fold protein such as antibody constant domains, transthyretin, beta-2 microglobulin, any serine protease inhibitors and crystalline would be useful as a method for minimizing the aggregation tendencies of *any* amyloid forming protein in vitro or in a cell.

For the reasons above, it would take an undue amount of experimentation for even one skilled in the art to practice the claimed invention. In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments and the declaration under 37 CFR 1.131 by Fred J Stevens filed 2/6/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims have been amended. (2) Newly added claims 21-22 are nearly identical to the Examiner's description of the enablement of the original specification.

However, the amended claims still recite a method of minimizing the aggregation tendencies of any amyloid protein. The specification does not teach a method for minimizing the aggregation tendencies of *any* amyloid forming protein other than human kappa-4 immunoglobulin light chain (LC). Further, the term "is" or "comprises" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is insufficient guidance and working examples as to which undisclosed amino acids to be added and (2) whether the resulting peptide when substitute into which undisclosed regions (residue numbers) of which undisclosed amyloid forming protein such as transthyretin, beta-2 microglobulin, *any* serine protease inhibitors and crystalline would prevent fibril formation in vitro or in a cell. As to claims 1, 17, 21 and 22, it is not clear if "LEN" and "SMA" represent the specific amino acids in human kappa-IV light chain or the "LEN" and "SMA" represent the mutation in the human kappa-IV light chain. There is insufficient guidance as to (1) the amino acid sequence of "SMA" or "LEN" and (2) which amino acid within the undisclosed full length amino acid sequence of SMA or LEN to be substituted. In fact, the declaration by Fred J Stevens states that the identified peptide is an eight amino acids peptide identical to positions 71 through 78 of the human kappa-4 light chain variable domain that demonstrates the ability to block fibril formation in vitro (PTO 892). However, works remains to validate the generality of the observation and is premature to argue that this peptide represents a useful drug. The declaration further states that the peptides of other sequence have been tested are not effective...the lack of activity by other peptides tested indicates structural specificity.

9. Claims 1-13, and 15-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** (1) a method for minimizing the aggregation tendencies of amyloid forming protein, the method comprising: a) identifying SMA or LEN mutation in the amino acid sequence of said protein that leads to fibril formation; b) substituting each mutation for Ala or proline into said LEN or SMA to identify the residues of a peptide that contribute to fibril formation; c) synthesizing peptides spanning most of the light chain variable region that interacts with an endoplasmic reticulum chaperone selected from the group consisting of Bip, Hsp 70 and combinations thereof; d) determining the VL-derived peptides for their ability to inhibit fibril formation in vitro wherein the peptides are selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR (SEQ ID NO: 12), LTLKSR (SEQ ID NO: 13) and combination thereof and e) **preventing** fibril or amyloid formation by inserting the said peptide in to the light chain variable domain, as set forth in claims 1-13, 15 and 16 and (2) a method for p**reventing** fibril assembly of human kappa-IV immunoglobulin as set forth in claims 17-22.

The specification discloses only for a method of minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in *vitro* by identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril formation, synthesizing peptides selected from the group consisting of spanning most of the Variable region of the LC that interacts with a endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, and determining the $V_L$-derived peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEEQ ID NO: 6), FTLEISR (SEQ ID NO: 12) and LTLKLSR (SEEQ ID NO: 13) for their ability to inhibit SMA fibril formation *in vitro*. The specification further discloses a method for minimizing the aggregation tendencies of human kappa-4 immunoglobulin light chain (LC) in a cell, the method comprises identifying the mutation in the amino acid sequence of said protein such as LEN and SMA, substituting each SMA mutation into LEN to identify the residues of a peptide that contribute to fibril aggregation, synthesizing peptides spanning most of the Variable region of the LC that interacts with a

endoplasmic reticulum chaperone selected from the group consisting of BiP and Hsp 70, expressing SMA or LEN in COS cells, treating said cells with said peptides selected from the group consisting of TDFTLTI (SEQ ID NO: 5), FTLTISS (SEQ ID NO: 1), FTLKISR (SEQ ID NO: 6), FTLEISR and LTLKLSR and determining the $V_L$-derived peptides for their ability to inhibit SMA fibril aggregation in said cell by western blotting or immunoflourosence.

With the exception of the specific methods for minimizing the aggregation of the specific amyloid forming protein such as human kappa-4 immunoglobulin light chain (LC) using the specific peptides derived from human kappa-4 immunoglobulin light chain (LC) mentioned above, there is insufficient written description about peptide because the term "is", "are" or "comprising" is open ended. It expands the peptide to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added and (2) whether the resulting peptide when substitute into which undisclosed regions (residue numbers) of which undisclosed amyloid forming protein such as transthyretin, beta-2 microglobulin, *any* serine protease inhibitors and crystalline would prevent fibril formation in vitro or in a cell.

As to claim 4, there is inadequate written description about which region of the light chain variable domain (i.e. specific amino acid residues) the undisclosed peptide is identical to, let alone inserting the undisclosed peptide between residue position numbers of 60 and 83 of human kappa-IV light chain when the protein is partially unfolded.

As to claim 6, the term "domain" needs clarification because the domain could be any domain in any Greek key fold protein such as antibody constant domains, transthyretin, beta-2 microglobulin, serine protease inhibitors and crystalline. The specification discloses only that the peptide consisting of the amino acid sequence $Phe_{71}$-$Thr_{72}$-$Leu_{73}$-$Thr_{74}$-$Ile_{75}$-$Ser_{76}$-$Ser_{77}$ (SEQ ID NO: 1) and wherein the subscript denote the positions of the amino acids in the light chain variable domain. Further, the peptide of SEQ ID NO: 1 is only seven amino acids in length derived from human kappa-IV immunoglobulin. There is insufficient written about the intact sequence of which protein that the subscripts denote.

As to claim 8, there is inadequate written description about the peptide such as SEQ ID NO: 5, 1, 6, 12 and 13 that is identical in composition to which portion of which protein that anchors a hairpin-shaped amino acid sequence to which Greek key fold protein.

As to claim 11, given the inadequate written description about the structure associated with function of the peptide (amino acid sequence), it follows that the undisclosed peptide is a

target for endoplasmic reticulum chaperone such as hsp70 and BiP in the claimed method is not adequately described.

As to claim 15, it is not clear which domain that the peptide Phe-THr-Leu-Thr-Ile-Ser-Ser is supposed to be inserted into. Further, the peptide recited in claim 15 is only seven amino acids in length. The subscript numbering 71 through 77 denotes the residues of the light chain variable domain of the full-length protein. However, the SEQ ID NO of the full-length human kappa-IV light chain is not recited in the claim.

As to claim 19, there is insufficient written description about the binding protein that binds to which region of which amino acid sequence in the claimed method.

As to claims 1, 17, 21 and 22, it is not clear if "LEN" and "SMA" represent the specific amino acids in human kappa-IV light chain or the "LEN" and "SMA" represent the mutation in the human kappa-IV light chain. There is inadequate written description about (1) the amino acid sequence of "SMA" or "LEN" and (2) which amino acid within the undisclosed full-length amino acid sequence of SMA or LEN to be substituted.

Given the lack of a written description of *any* additional representative species of peptide derived from other amyloid forming protein or Greek key fold protein such as antibody constant domains, transthyretin, beta-2 microglobulins, any serine protease inhibitors and crystalline for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 2/6/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) claims have been amended. (2) Newly added claims 21-22 are nearly identical to the Examiner's description of the enablement of the original specification.

However, the amended claims still recite a method of minimizing the aggregation tendencies of any amyloid protein. The specification does not teach a method for minimizing the aggregation tendencies of *any* amyloid forming protein other than human kappa-4

immunoglobulin light chain (LC). Further, the term "is" or "comprises" is open-ended. It expands the peptide to include additional amino acids at either or both ends. There is inadequate written description about which undisclosed amino acids to be added and (2) whether the resulting peptide when substitute into which undisclosed regions (residue numbers) of which undisclosed amyloid forming protein such as transthyretin, beta-2 microglobulin, *any* serine protease inhibitors and crystalline would prevent fibril formation in vitro or in a cell. As to claims 1, 17, 21 and 22, it is not clear if "LEN" and "SMA" represent the specific amino acids in human kappa-IV light chain or the "LEN" and "SMA" represent the mutation in the human kappa-IV light chain. There is inadequate written description about (1) the amino acid sequence of "SMA" or "LEN" and (2) which amino acid within the undisclosed full-length amino acid sequence of SMA or LEN to be substituted. Given the lack of a written description of *any* additional representative species of peptide derived from other amyloid forming protein or Greek key fold protein such as antibody constant domains, transthyretin, beta-2 microglobulins, any serine protease inhibitors and crystalline for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1-8, 10-13 and 15-22 are rejected under 35 U.S.C. 102(a) as being anticipated by Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892).

Davids *et al* teach a method for minimizing or preventing the aggregation or fibril assembly of an amyloid forming protein such as human immunoglobulin light chain variable domain (See entire document, in particular). The reference method involves identifying the mutation in the amino acid sequence of the human immunoglobulin kappa IV light chain variable domain such as LEN k chain and SMA and REC kappa chain and test their ability to bind to binding protein such as BiP under physiological conditions (See page 3844, binding of $V_L$ domains of LC to BiP, page 3845, Identifying Potential BiP binding sites in $V_L$, in particular), replacing the amino acid residues that contact the bound peptide in BiP, testing the peptides

derived from human immunoglobulin light chain variable domain for their ability to compete with the binding of the labeled peptide such as TDFTLTI and FTLTISS to BiP (See page 3847, column 1, last paragraph, in particular). Davids *et al* teach the reference method can be conducted in vivo by expressing the human immunoglobulin kappa light chain variable domain such as LEN k chain, SMA, or REC kappa chain in COS cell. The reference peptides such as TDFTLTI and FTLTISS have amino acid sequences identical to an amino acid sequence in a region such as 69-75 and 71-77, respectively, of the light chain variable domain (See Table 1, in particular). The reference method wherein the peptide binds between residue position number 60 and 83 of the protein such as the human immunoglobulin light chain variable domain (See Table 1, in particular). The reference method wherein the peptide is 100% identical to the claimed sequence $Phe_{71}$-$Thr_{72}$-$Leu_{73}$-$Thr_{74}$-$Ile_{75}$-$Ser_{76}$-$Ser_{77,}$ wherein the subscripts inherently denoted the positions of the amino acids in the variable domain of the reference human immunoglobulin kappa light chain variable domain (See page 3847, column 1, in particular). The reference method wherein the peptide inherently binds to the human immunoglobulin kappa light chain variable domain when it is partially unfolded in the endoplasmic reticulum as long as they have not completed their disulfide bonding (See page 3848, column 2, last paragraph, in particular). The reference method wherein the peptide is identical in composition to a portion of a protein such as $V_L$ that anchors a hairpin-shape amino acids to the protein and the reference peptide such as TDFTLTI and FTLTISS is inserted at a hairpin anchorage point in the Greek key fold protein (See Fig 4, in particular). The reference method wherein the peptide such as TDFTLTI and FTLTISS interact with endoplasmic reticulum chaperone such as hsp70 and BiP (See page 3842, column 1, Fig 3, in particular). The reference method also prevent fibril assembly such as identifying the region of the human immunoglobulin kappa light chain variable domain (fist aggregating protein) that normally interacts with a binding protein such as the BiP and juxtaposing the reference binding protein by exposing the BiP protein to the human immunoglobulin kappa light chain variable domain (first aggregating protein) in the present of the reference peptides such as TDFTLTI and FTLTISS derived from immunoglobulin light chains (second protein moiety) where the reference BiP binding protein binds to a region within the immunoglobulin light chains (See page 3844, binding of $V_L$ domains of LC to BiP, page 3845, Identifying Potential BiP binding sites in $V_L$, See Table 1, in particular). Thus, the reference teachings anticipate the claimed invention.

Applicants' arguments and the affidavit under 37 CFR 1.131 by Fred J Steven filed 2/6/03 have been fully considered but are not found persuasive for reasons stated above. The evidence submitted is insufficient to establish a reduction to practice of the invention in this country prior to the effective date of the Davids reference because (1) the scope of the affidavit is not commensurate with the scope of the claims and (2) missing the signatures of inventors Fred J. Stevens, Yair Argon and Rosemarie Raffen.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892) in view of Gardner *et al* (J Biol Chem 268(34): 25940-47, 1993; PTO 892), Schubert *et al* (European J Neuroscience 9: 770-777, 1997; PTO 892) or Ohashi *et al* (Virchows Arch 428(1): 37-46, 1996; PTO 892).

The teachings of Davids *et al* have been discussed supra.

The claimed invention as recited in claims 3 and 9 differs from the references only by the recitation that the protein is serine protease inhibitor.

The claimed invention as recited in claim 9 differs from the references only by the recitation that the protein is beta-2-microglobulin.

Gardner *et al* teach a serine protease inhibitor such as 3,4-DCI that protects newly synthesized immunoglobulin light chain from degradation (See page 25944, column 2, k Chain Degradation Is Inhibited by Serine Protease Inhibitors, Fig 8, in particular).

Schubert *et al* teach a serine protease inhibitor such as Serpins that inhibits amyloid peptides aggregation and toxicity (See entire document, page 771, column 2, Serpins inhibits amyloid and amylin toxicity and aggregation, in particular).

Ohashi *et al* teach beta-2-microglobulin amyloidosis associated with long-term heamodialysis which has an increased in matrix metalloproteinases such as MMP-1, while AL amyloidosis is involved in immunoglobulin light chain deposits in the particular tissues (See abstract, page 44, column 2, in particular). Ohashi *et al* teach serine proteinases have been implicated in the degradation of extracellular matrix components and various proteinase inhibitors are useful for inhibiting joint destruction (See page 37, column 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit serine proteinase using proteinase inhibitor such as 3,4-DCI as taught by Gardner *et al* or the Serpins as taught by Schubert *et al* for a method of minimizing the aggregation any amyloid forming protein such as immunoglobulin light chain as taught by Davids et al or the beta-2-microglobulin as taught by Ohashi *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Gardner *et al* teach serine protease inhibitor such as 3,4-DCI can protect newly synthesized immunoglobulin light chain from degradation (See page 25944, column 2, k Chain Degradation Is Inhibited by Serine Protease Inhibitors, Fig 8, in particular). Schubert *et al* teach serine protease inhibitor such as Serpins can inhibit amyloid peptides aggregation and toxicity (See entire document, page 771, column 2, Serpins inhibits amyloid and amylin toxicity and aggregation, in particular). Ohashi *et al* teach serine proteinases have been implicated in the degradation of extracellular matrix components and various proteinase inhibitors are useful for inhibiting joint destruction and beta-2-microglobulin amyloidosis associated with long-term heamodialysis that has an increased in matrix metalloproteinases such as MMP-1 (See page 37, column 2, in particular).

15. Claims 1 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davids *et al* (J Immunology 163: 3842-50, Oct 1999; PTO 892) in view of US Pat No. 5,276,059 (Jan 1994; PTO 892).

The teachings of Davids *et al* have been discussed supra.

The claimed invention as recited in claim 9 differs from the references only by the recitation that the protein is selected from the group consisting of antibody constant domains and transthyretin.

The '059 patent teaches protein such as transthyretin is involved with Familial amyloid polyneuropathy, beta-2-microglobulin is involved with amyloidosis or fibril aggregation associated chronic dialysis, immunoglobulin constant domain (IgG 1 (γ1) is involved with macroglobulin or idiopathic (primary) myeloma (See Table 1, column 5, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunoglobulin light chain as taught by Davids *et al* for the beta-2-microglobulin or immunoglobulin constant domain or the transthyretin as taught by the '059 patent for a method of minimizing the aggregation tendencies of any amyloid forming protein. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '059 patent teaches any protein such as beta-2-microglobulin or immunoglobulin constant domain or the transthyretin can form amyloid deposits and inhibition of amyloid deposit is beneficial in the treatment and prevention of these diseases (See column 5, lines 5-7, in particular).

16. The following new grounds of objection and rejection are necessitated by the amendment filed 2/6/03.

17. Claim 21 is objected to because the article "A" is missing. It should have been "A method..."

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

19. Claims 1-13, 17-20, and 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "SMA or LEN" in amended claims 1, 17, and newly submitted claims 21 and 22 is indefinite and ambiguous because it is not clear "SMA or LEN" stands for, much less about the amino acid sequences of said SMA or LEN. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

"The binding protein" in claims 19 and 20 has no antecedent basis in base claim 17. Base claim 17 requires the endoplasmic reticulum chaperone BiP and Hsp 70 be bind to the variable region of the light chain.

The "an amino acid sequence that is the same as the amino acid sequence of the region" in claim 20 is ambiguous and indefinite because it is not clear as to which amino acid sequence of which binding protein that is the same as the amino acid sequence of which undisclosed region.

The "peptide is an endoplasm reticulum selected from the group consisting of hsp70 and BiP" in claim 12 is ambiguous and indefinite because the peptides as set forth in based claim 1 are variable light chain-derived peptides and not hsp70 and BiP, the endoplasmic reticulum chaperone. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention. Appropriated correction is required.

The "LEN" and "SMA" in claims 1, 17 and 21-22 are ambiguous and indefinite because it is not clear if "LEN" and "SMA" represent amino acids or what "LEN" and "SMA" stand for. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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October 20, 2003

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